Serial Changes in Alpha-Fetoprotein Levels During Therapy for Chronic Hepatitis C

Kronik Hepatit C Tedavisi Sırasında Alfa-Feto Protein Düzeylerindeki Seri Değişiklikler

Alpha-Fetoprotein Levels in Chronic Hepatitis C

Altuğ Şenol[1], Mete Akın[2], Yıldıran Songür[3], Mehmet İşler[4], M.Cem Koçkar[1]
[1]Süleyman Demirel University School of Medicine, Department of Gastroenterology, Isparta,
[2]Akdeniz University School of Medicine, Department of Gastroenterology, Antalya,
[3]Memorial Şişli Hospital, Department of Gastroenterology, İstanbul,
[4]Şifa Hospital, Department of Gastroenterology, Isparta, Turkey

Özet

Amaç: Alfa-feto protein (AFP) hepatosellüler karsinom tanısı için yaygın olarak kullanılan bir belirteçtir. Bazı hepatit C'li hastalar, yüksek AFP değerleri sergilemekte ancak hepatosellüler karsinom kanıtı bulundurmamaktadırlar. Bu çalışmanın amacı, hepatosellüler karsinomu bulunmayan kronik hepatit C'li hastalarda serum AFP üzerinde antiviral tedavinin etkisini değerlendirmektir. Gereç ve Yöntem: Kronik hepatit C'li otuz yedi hasta (20 kadın ve 17 erkek) bu çalışmaya dahil edildi. Tüm hastalara pegile veya konvansiyonel IFN ve ribavirin kombinasyon tedavisi verildi. Serum AFP bazal değerde ve tedavinin 3-6-12. aylarında ölçüldü. Bulgular: ALT düzeyinin tedavi öncesi ile karşılaştırıldığında (88,59 ± 57.22 IU) 3,6 ve 12. aylardaki düzeyleri istatistiksel olarak daha düşüktü (p< 0.001). Ortalama serum AFP düzeyleri yavaş yavaş tedavi öncesindeki 6,6 ± 6,05 ng/ml düzeyinden sırasıyla 3. ayda 5,1 ± 3,7 (p>0,05), 6. ayda 4,34 ± 4,64 (p>0,05) ve 12. ayda 2,63 ± 2,17 (p<0,001) düzeylerine indi. AFP düzeyi yüksek olan hastalarda (>10 ng/ml) 3. ayda istatistiksel olarak anlamlı olmayan düşme gözlenirken; 6. ve 12. aylarda istatistiksel olarak anlamlı oranda düşüş gözlendi. Bu hastalarda ortalama serum AFP düzeyleri 3, 6 ve 12. aylarda sırasıyla 11,39±3,30, 6,97±2,53 (p<0,001) ve 5,67±3,89 (p=0,009)'dı ve tedavi öncesi değer olan 15,09 ± 5,92 ng/ml'e göre düşüktü. Tartışma: Serum AFP düzeyi 48 hafta boyunca interferon-α ve ribavirin alan hepatit C'li hastalarda tedavi sırasında anlamlı derecede azalmaktadır.

Anahtar Kelimeler

Kronik Hepatit C; Alfa-Fetoprotein; İnterferon Alfa; Ribavirin

Abstract

Aim: Alpha-fetoprotein (AFP) has been widely used as a diagnostic marker for hepatocellular carcinoma. Some patients with hepatitis C show high AFP values, but no evidence of hepatocellular carcinoma. The aim of this study is to assess the influence of antiviral treatment on the serum AFP in patients with chronic hepatitis C without hepatocellular carcinoma. Material and Method: Thirty seven chronic hepatitis C patients (20 females and 17 males) were included in the study. All patients were given a combined treatment of pegylated or conventional interferon (IFN) and ribavirin. Serum AFP was measured at baseline and on months 3-6-12 of the therapy. Results: Compared to the pretreatment levels of ALT (88,59 ± 57,22 IU), those at 3, 6 and 12 months were statistically lower (p< 0,001). Mean serum AFP levels gradually decreased from pretreatment level of 6,6 ± 6,05 ng/ml to 5,1 ± 3,7 (p>0,05), to 4,34 ± 4,64 (p>0,05) and to 2,63 ± 2,17 (p<0,001) at month 3, 6 and 12 of the therapy, respectively. Although AFP decrease at month 3 was non significant, a significant decrease of mean serum AFP levels after 6 and 12 months of therapy was demonstrated in the patients with high AFP (>10 ng/ml). In these patients, mean serum AFP levels were decreased from pretreatment level of 15,09 ± 5,92 ng/ml to 11,39±3,30, to 6,97±2,53 (p<0,001) and to 5,67±3,89 (p=0,009) at month 3, 6 and 12, respectively. Discussion: Serum AFP level significantly decreases during therapy in hepatitis C patients receiving IFN-α plus ribavirin for 48 weeks.

Keywords

Chronic Hepatitis C; Alpha-Fetoprotein; Interferon Alfa; Ribavirin

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Corresponding Author: Mete Akın, Akdeniz University Hospital, Department of Gastroenterology, Antalya, Turkey.
T.: +90 2422496000 E-Mail: drmeteakin@hotmail.com

Introduction

Mortality due to hepatitis C infection is associated with decompensated cirrhosis and the development of hepatocellular carcinoma [1, 2]. Persistent hepatitis C infection is a major risk factor for development of hepatocellular carcinoma, and inhibition of hepatocarcinogenesis remains a crucial issue in treating patients with chronic hepatitis C [3]. Currently, combination therapy of interferon-α or pegylated interferon-α with ribavirin has become the standard of therapy for chronic hepatitis C with a rate of sustained response of approximately 45% with conventional interferon-α and approximately 60% with pegylated interferon-α [4-7]. Since, interferon harbors antiviral, anti-inflammatory, and anticancer effects, it has been assumed to have a preventive effect on the development of hepatocellular carcinoma, especially in patients with sustained virological response [8-13]. Explaining how a transient improvement in liver function tests induced by interferon treatment reduces the incidence of hepatocellular carcinoma during the progression of chronic hepatitis to cirrhosis is difficult, because it requires many years [3].

Alpha-fetoprotein (AFP), a glycoprotein with a molecular weight of approximately 70 kD has been widely used as a diagnostic marker for hepatocellular carcinoma. The diagnosis of hepatocellular carcinoma is generally made in patients with a mass lesion in a cirrhotic liver if the AFP is over 400 ng/ml [14-15]. However, some patients have an elevated AFP, but no evidence of hepatocellular carcinoma that could be found after a thorough radiologic evaluation [16-18]. Several reports have demonstrated a decrease in the elevated AFP after interferon-α therapy in patients with chronic hepatitis C without a mass lesion in the liver [19-21].

The present study aimed to investigate the serial changes of serum AFP levels during therapy in chronic hepatitis C patients receiving interferon-α plus ribavirin for 48 weeks.

Material and Metod

This study was conducted between the years of 2003-2008 in the Gastroenterology Clinic of Süleyman Demirel University School of Medicine, Isparta, Turkey. The study group consisted of 37 patients (20 females, 17 males, mean age: 49,9 years, range 21-68) with chronic hepatitis C. Serum HCV-RNA was positive in all patients. All patients had undergone liver biopsy which consistent with chronic hepatitis C. None of them was positive for hepatitis B surface antigen and anti-HIV. No patient had received immunosuppressive therapy.

Seventeen patients were treated with peginterferon -2b (1.5 µg/kg sc once weekly) or peginterferon -2a (180 µgr sc once weekly) and ribavirin (1000 mg daily for < 75 kg body weight and 1200 mg daily for >75 kg body weight). Twenty patients were treated with conventional interferon- 2b or interferon-α 2a (3×106 MU 3 thrice weekly) and ribavirin (1000 or 1200 mg daily according to body weight). Interferon/ribavirin therapy was stopped in patients whom HCVRNA was positive in six months of therapy or in patients whom HCVRNA did not decrease 2 log in three months of therapy.

All patients completed the interferon-α treatment for at least 80% of the full dosage. Ribavirin dosages were adjusted according to periodical hemoglobin checkups and clinical symptoms of anemia. Blood tests including complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, protrombin time, and AFP were obtained before starting the treatment, and 3,6 and 12 months of the therapy.

The Real-time PCR method with Robo Gene (Roboscreen, Leipzig, Germany) kits in ABI PRISM 7700 (Applied Biosystems) device HCV-RNA was used. Serum levels of AFP were measured by chemiluminesence technique with Immulite 2000 autoanalyser (Diagnostic Products Corp., USA).

All patients were examined by abdominal ultrasonography before and after the therapy. Computed tomography examination was performed in the patients with elevated AFP level. No mass lesion could be demonstrated in the patients.

2.1. Statistical analysis

Results were subjected to routine statistical analysis using the computer program SPSS (version 11.0) with significance level set at $P < 0.05$. Paired-t test, Wilcoxon test, Mann–Whitney's U-test and Fisher exact test were applied where appropriate. The results are expressed as mean ± standard deviation and median (min-max).

Results

There were 20 female and 17 male patients and mean age was 49,97 ± 9,25 years. Biochemically, 32 (86,4 %) patients had elevated ALT. The mean pretreatment ALT was 88,59 ± 57,22 IU (Table 1). 33 patients had normal ALT levels at the end of 3, 6 and 12 months of therapy, respectively. Compared to the pretreatment levels of ALT, those at 3, 6 and 12 months were statistically lower (p< 0,001). The mean pretreatment AST was 67,67 ± 35,98 IU (Table 1). Compared to the pretreatment levels of AST, those at 3, 6 and 12 months were statistically lower (p< 0,001). The therapy was stopped in 3 patients who had elevated ALT levels at the 6 months of therapy while HCV-RNA was still detectable.

Table 1. AFP, ALT, AST levels at baseline, 3, 6 and 12 month, and HCV load, histologic activity index, fibrosis scores (mean ± SD) of patients

		p
Baseline AFP (ng/ml)	6,60 ± 6,05	
AFP month 3 (ng/ml)	5,10 ± 3,70	0,065
AFP month 6 (ng/ml)	4,34 ± 4,64	0,063
AFP month 12 (ng/ml)	2,63 ± 2,17	<0,001
Baseline ALT (IU)	88,59 ± 57,22	
ALT month 3 (IU)	23,89 ± 19,89	<0,001
ALT month 6 (IU)	26,37± 22,17	<0,001
ALT month 12 (IU)	24,55 ± 21,45	<0,001
Baseline AST (IU)	67,67 ± 35,98	
AST month 3 (IU)	29,68 ± 13,94	<0,001
AST month 6 (IU)	29,84 ± 14,23	<0,001
AST month 12 (IU)	26,91 ± 13,79	<0,001
Baseline		
HCV-RNA (copies/ml)	2602906 ± 6646350	
Histologic activitiy index (HAI)	8,86 ± 3,88	
Fibrosis staging		
Stage 1-2	22 (%59,5)	
Stage 3-4	15 (%40,5)	

INR: international normalized ratio, AFP: Alpha-fetoprotein, ALT :alanine aminotransferase, AST:aspartate aminotransferase.

In the patients with chronic hepatitis C, after treatment with interferon-α and ribavirin, AFP decreased in this study. Mean serum AFP levels were presented in month 3 and month 6 of the therapy were presented Table 1. Compared with baseline AFP levels, those at 3 and 6 (p=0,065, 0,063) months were not statistically significant. A significant decrease of mean serum AFP levels after 12 months of antiviral therapy compared to pretreatment AFP levels were demonstrated (p<0,001) (Table 1).

Based on the pretreatment AFP results, the patients were classified into two groups (Table 2). Pretreatment serum AFP level was below 10 ng/dl (Group 1) in 28 patients (16 females, 12 males). Pretreatment serum AFP level was above 10 ng/dl (Group 2) in 9 patients (5 females, 4 males). The baseline characteristics of the two groups, including age and pretreatment ALT level were similar (Table 2). Mean AFP level was 3,87 ± 2,60 ng/dl in group 1, and 15,09 ± 5,92 in group 2 (p<0,001). The percentage changes of the two groups are presented in table 2.

Histological examination of the liver biopsies revealed an histologic activity index (HAI) < 7 in 13 (35,1%) patients, and an HAI ≥7 in 24 (64,8%) patients. Twenty-two patients (59,4%) had stage 1-2 fibrosis, while 15 (40,5%) patients had stage 3-4 fibrosis. The majority of group 2 patients had an HAI ≥7 and stage 3-4 fibrosis, 88,9% and 77,8%, respectively. There was not a significant difference between the HAI scores of group 1 and group 2. A statistically significant difference between fibrosis stages of group 1 and 2 was noted (p=0,017) (Table 2).

Table 2. Comparison of demographic and laboratory values of patients due to normal and elevated serum AFP levels at baseline.

	AFP <10 ng/ml n= 28 (Group 1)	AFP >10 ng/ml n=9 (Group 2)	p
Baseline INR	1.05 ± 0.11	1.15 ± 0.06	0.135
AFP (ng/ml)			
Baseline	3.87 ± 2.60	15.09 ± 5.92	
Month 3	3.53 ± 1.34	11.39 ± 3.30	
Month 6	24.89 ± 23.07	6.97 ± 2.53	
Month 12	2.07 ± 1.16	5.67 ± 3.89	
ALT (IU/L)			
Baseline	81.18 ± 54.49	106.78 ± 67.31	0.279
Month 3 *	-0.72 (-0.9/0.23)	-0.74 (-0.81/-0.03)	0.641
Month 6 *	-0.75 (-0.94/0.77)	-0.75 (-0.82/-0.08)	0.565
Month 12 *	-0.75 (-0.94/1.00)	-0.71 (-0.84/-0.66)	0.879
AST (UI/L)			
Baseline	62.75 ± 35.83	84.88 ± 32.95	0.127
Month 3 *	-0.51 (-0.98/1.00)	-0,45 (-0.75/0.03)	0.489
Month 6 *	-0.54 (-0.82/0.47)	-0,59 (-0.74/1.00)	0.896
Month 12 *	-0.95 (-0.95/1.00)	-0.69 (-0.73/0.18)	0.755
HCV-RNA(copies/ml)	2720162±7554827	2238111±2440400	0.853
<106	11 (%67.9)	5 (%55.6)	
≥106	9 (%32.1) 4 (%44.4)		
Histology activity index	8.43 ± 3.93	10.22 ± 3.60	0.159
<7	12 (%42.9)	1 (%11.1)	
≥7	16 (%57.1)	8 (%88.9)	
Fibrosis-staging			0.017
1-2	20 (%71.4)	2 (%22.2)	
3-4	8 (%28.6)	7 (%77.8)	

* The percent change presented as median [min/max]) AFP: Alpha-fetoprotein, ALT : alanine aminotransferase, AST:aspartate aminotransferase

Discussion

We found that AFP gradually decreased with the treatment of chronic hepatitis C. However, the change in AFP level became significant after 12 month-therapy. In the patients with high pre-treatment AFP level, the change in AFP level was significant at the 6th month of the therapy. The reported prevalence of elevated AFP in patients with chronic hepatitis C varied from 10% to 43% [16, 17, 22, 23]. The pathogenesis and clinical significance of the mild elevated AFP remain to be defined, although some studies have demonstrated that elevation of serum AFP is associated with increased transaminase, severe fibrosis, genotype 1b, and cirrhosis [16-18, 23, 24]. Furthermore, it is unclear whether such mild elevation of serum AFP is associated with eventual development of hepatocellular carcinoma in chronic hepatitis C patients. Hepatocarcinogenesis is closely related to the presence of chronic hepatitis with advanced liver fibrosis, which represents a pre-cancerous state accompanied by increased DNA synthesis [3]. In fact, it has been suggested that cirrhotic patients with high liver cell proliferative activity are more likely to develop hepatocellular carcinoma as compared with those without it [3, 25].

An increased serum ALT level reflects a higher hepatitis activity. A higher hepatocellular carcinoma recurrence rate after hepatectomy has been observed in patients with hepatitis activity [26, 27]. This result suggests that the higher risk of hepatocellular carcinoma recurrence observed in patients with chronic hepatitis C reflects these patients having a higher degree of hepatitis activity related to the elevated carcinogenesis [27]. Probably, severe inflammation causes liver cell necrosis and cytolysis with persistent high ALT levels. During subsequent process of liver cell regeneration, the cell proliferative activity is abnormally enhanced and it is accompanied with an elevation of AFP levels, which eventually to hepatocellular carcinoma [28]. Our results may support this hypothesis. Because, in this study, the majority of the patients with high AFP level had a HAI of more than 7. ALT levels were decreased to normal ranges at the 3, 6 and 12 months of therapy in majority of the patients. The decrease in ALT level was associated with the clearance of HCVRNA and also decrease in AFP level. When the fibrosis score was analysed, it was noted that 77,8% of the patients with high AFP level had a fibrosis score of 3-4 whereas only 28,6 % of the patients with less than 10 ng/ml AFP level had a fibrosis score of 3-4 in our study. Since, AST correlates with fibrosis, fibrosis seems to be a more important factor than HAI on the AFP level.

The effects of combined therapy on hepatocellular carcinoma were investigated in several studies [29]. In one prospective, controlled trial, 100 patients were randomized to receive either interferon-α or were followed-up without treatment. After a 2- to 7-year period of follow-up evaluation, hepatocellular carcinoma was significantly reduced in the treated group (4%) as compared with the nontreated controls (38%) [8]. Kasahara et al also have reported that responders to interferon treatment with decreased ALT had a lower risk of hepatocellular carcinoma development [30].

Although, there has been some debate on the cut-off level of AFP, an elevated AFP or a progressively increasing trend in AFP reflects a patient subgroup with high risk for development of hepatocellular carcinoma [31]. Because, an increasing trend in

AFP has been observed only in patients developing hepatocellular carcinoma, Farinati et al. suggested that hepatocellular carcinoma should be investigated in patients who have progressively increasing trend of AFP below 20 ng [32]. These results suggest that the progressive changes in serial AFP levels may be important. It may be speculated that a decreasing trend in a progressive manner in AFP may be evidence of reversing of the sequence for hepatocarcinogenesis. Taken together, both liver fibrosis and increased hepatitis activity may lead to the development of hepatocellular carcinoma as a consequence of a sustained necroinflammatory reaction [27], a decrease in AFP level may be related to prevention of severe inflammation causing liver cell necrosis and cytolysis and decrease in subsequent liver cell regeneration and cell proliferative activity by interferon-ribavirin therapy [33].

In conclusion, serum AFP level is significantly decreased during the therapy in chronic hepatitis C patients receiving interferon-α plus ribavirin for 48 weeks. Long-term follow-up of the HCV-infected patients can show if such decrease of serum AFP is associated with eventual decrease in development of hepatocellular carcinoma.

Competing interests

The authors declare that they have no competing interests.

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